EXHIBIT B

U.S. FOOD & DRUG ADMINISTRATION

May 03, 2023

Institution Name: Columbia University Irving Medical Center

Attention: Lena Sun

Subject: Request for Full Proposal, Broad Agency Announcement for the U.S. Food and Drug Administration (FDABAA-23-00123)

Dear Lena Sun:

The U.S. Food and Drug Administration (FDA) has completed the review of your Quad Chart and White paper:

Health and Neurodevelopmental Outcomes in Infants at Risk for Neonatal Opioid Withdrawal Syndromes (NOWS): Effects of Timing and Duration of Prenatal Opioid Exposure (POE) & Postnatal Management with Eat-Sleep-Console (ESC)

We are pleased to inform you that after careful consideration of your Quad Chart and White Paper, you are invited to submit a full proposal. The guidelines for the preparation of the full proposal are described in the BAA Part III.

The following technical feedback from the review of your white paper is provided to further guide you in the formulation of your full proposal. Please note that since multiple reviewers contributed to the guidelines below, some redundancies in comments provided present multiple view points for clarity:

1. *The study topic is a high priority area in regulatory science, however some of the study aims do not have a clear regulatory impact. We recommend reframing the study aims to focus on determining differences of non-pharmacologic (i.e., Eat-Sleep-Console) vs. pharmacologic treatment on NOWS outcomes.*
2. *Retrospective studies are a useful option for gathering and evaluating data from a difficult-to-recruit and difficult-to-treat population. However, they have certain limitations and can introduce biases, such as in recordkeeping. To strengthen this proposal, we recommend re-scoping the study to add a small prospective cohort of cases to follow, based on the same criteria as retrospective data, and evaluate whether your findings from the retrospective studies can predict or inform treatment outcomes.*
3. *In addition to including timing and duration as measures of exposure, consider adding dosage information as a predictive variable. Dosage may act as a moderating or mediating variable and could make the results difficult to interpret if not controlled for. In addition, explain how maternal dose of opioid analgesic*

prescriptions or medications for opioid use disorder (e.g., buprenorphine or methadone) would be treated in the exposed groups.

4. *The proposal identifies that concomitant exposure with controlled substances and psychotropic medications may be a confound. Explain how this potential confound will be addressed.*
5. *Consider additional metrics for early neurodevelopmental outcomes. The listed outcomes for neurodevelopment may not be diagnosable until after age two. Earlier measures, such as qualification for Early Intervention services (e.g., speech therapy, physical therapy), may serve as earlier, clinically meaningful outcome variables.*
6. *In the full proposal, identify and provide a plan for filling specific support staff roles. The speed and quality of hires for data analysis, project management, and research assistance will impact the project timeline and its overall success. Additionally, include a description of study limitations, provide a brief description of the statistical analysis plan, such as power analysis and statistical test(s) for experimental goals involving hypothesis testing, and describe plans for study documentation.*
7. *Because FDA's funding is contingent on Congressional appropriations, it would be helpful to include an outline of one or more deliverables per each year of funding.*

Additionally, in accordance with Part III, Section 4 (A) and (C) of the BAA, in order to provide the Government with greater flexibility regarding technical needs and funding constraints, you are encouraged to structure your proposal with severable/stand-alone deliverables to the extent it is practicable with the research being proposed. Your cost proposal shall clearly identify the costs associated with each task to be completed and whether or not they are proposed as part of a single, non-severable undertaking, or as part of a severable deliverable.

Thank you for your continued interest in the BAA. We look forward to receiving your full proposal. Your proposal must be signed by an individual who is authorized to legally commit your institution to any subsequent offer. Please submit your full proposal no later than 3:30pm ET, June 02, 2023, in accordance with the BAA.

Please send one electronic copy of the full proposal by the date and time specified above to the following email addresses:

FDABAA@fda.hhs.gov
Ingrid.Walker@fda.hhs.gov

Attention: Ingrid Walker, Contract Specialist
Reference: FY23C3DWP3

Please note that in order to be considered for award, your organization must be registered in the System for Award Management (SAM) in accordance with FAR 4.1102.

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If you have any questions, please contact FDABAA@fda.hhs.gov

Sincerely,

Ingrid Walker
Contract Specialist